SUPPLEMENTAL MATERIAL

Supplemental Table S1. Phenotype assays used in each cohort.

Phenotype	Cohort	Assay Description
FVII level	ARIC	Factor VII activity was measured by determining the ability of the tested sample to correct the clotting time of human factor VII– deficient plasma obtained from George King Biomedical Inc. (Overland Park, KS). Plasma activity level was determined by relating the clotting time to a calibration curve constructed with each assay. Values were expressed as percentage of the standard. The reliability coefficient obtained from repeated testing of 39 individuals over several weeks was 0.78, and the method CV was 7.3%. No reference range available.
	CHS	Factor VII activity was determined by using factor VII-deficient plasma (Baxter-Dade, Bedford MA, USA) and Thrombrorel S (Behring Diagnostics, Marburg, Germany) human-placenta derived thromboplastin. Activity measured using Coag-A-Mate X2 (Organon-Teknika, Durham, NC). Values were expressed as percentage of the standard. The intra-assay CV was 5.6% and inter-assay CV was 6.2%. No reference range available.
	FHS	Factor VII antigen levels were determined by ELISA (Diagnostica Stago). Values were expressed as percentage of the standard. The intra-assay CV was 3.0%. No reference range available.
	RS	Factor VII activity was measured with a one-stage clotting assay by using human thromboplastin (Tromborel S, Siemens) and factor VII-deficient plasma (Ortho Diagnostic System). The plasma concentrations were expressed as percentage activity by relating the clotting time to a calibration curve constructed of a standardized control plasma. As a control, the pooled plasma of 50 healthy middle-aged persons was used and three control samples were run with each batch of study samples. The intra-assay CV was 1.7%, the inter-assay CV was 3.7%, and reference range was 0.60-1.40 U/ml.
	Twins UK	For Twins UK-1, factor VII activity was measured using a functional clotting assays were chosen factor VII with a prothrombin-time based clotting assay with factor VII-deficient plasma on an ACL300 research coagulometer (Instrumentation Laboratory, Milan, Italy). For Twins UK-2, factor VII antigen level was determined by ELISA.
	PROCARDIS	Factor VII antigen was measured with a sandwich ELISA using a matched-pair antibody set from Affinity Biologicals Inc (Ancaster, ON, Canada). The plasma concentration was expressed in U/mL by relating the absorbance of the sample to that of a calibration curve constructed with a standardized coagulation reference plasma (Technoclone GmbH, Vienna, Austria). Normal control plasma for coagulation analyses (Global Hemostasis Institute, Linköping, Sweden) was used for assessment of the variability of the asssay, rendering an intra-assay CV of 8% (n=10) and an inter-assay CV of 10% (n=41).
FVIII level	ARIC	FVIII activity was measured by assessing clotting time after adding factor VIIII deficient plasma obtained from George King Biomedical Inc. (Overland Park, KS). Plasma activity level was determined by relating the clotting time to a calibration curve constructed with each assay. Values were expressed as percentage of the standard. The reliability coefficient obtained from repeated testing of 39 individuals over several weeks was 0.86, and the method CV was 5.9%. No reference range available.
	CHS	FVIII activity determined by using factor VIII-deficient plasma (Organon-Teknika) and partial thromboplastin (Organon-Teknika). Unassayed pooled normal plasma (George King Biomedical, Overland Park, KS, USA) was used as the standard and calibrated with the World Health Organization reference plasma for both assays. Activity measured using Coag-A-Mate X2 (Organon-Teknika). Values were expressed as percentage of the standard. The intra-assay CV was 12.6% and inter-assay CV was 13.8%. No reference range available.
	RS	Factor VIII activity was measured with a one-stage clotting assay by using a mixture of micronized silica and

		phospholipids (Platelin LS, Biomerieux) and factor VIII-deficient plasma (Biopool). The plasma concentrations were expressed as percentage activity by relating the clotting time to a calibration curve constructed of a standardized control plasma. As a control, the pooled plasma of 50 healthy middle-aged persons was used and three control samples were run with each batch of study samples. The intra-assay CV was 2.9%, the inter-assay CV was 5.2%, and the reference range was 0.70-1.40 U/ml.
	Twins UK	Factor VIII antigen was measured using ELISA (Immuno, Vienna, Austria) methods.
vWF level	ARIC	Von Willebrand factor antigen was determined by an enzyme-linked immunosorbent assay (ELISA) kit from American Bioproducts Co (Parsippany, NJ). The reliability coefficient obtained from repeated 39 testing of individuals over several weeks was 0.68, and the method CV was 18.5%. No reference range available..
	B58C	Plasma von Willebrand factor antigen levels were measured using an in-house enzyme linked immunosorbent assay (ELISA), employing rabbit anti-human polyclonal antibodies obtained from DAKO plc, Copenhagen, Denmark. The standard curve was constructed using the 9th British standard for Blood Cogulation Factors from National Institute for Biological Standards and Controls (NIBSC), South Mimms, Herefordshire UK, and the results were expressed as International units/decilitre(IU/dl). As a control, the pooled plasma of 20 healthy middle-aged persons was run on each ELISA plate. The intra-assay CV was 6%, the inter-assay CV was 8%, and reference range was 50 to 200 IU/dl.
	VIS	Same as B58C
	ORCADES	Same as B58C
	FHS	Von Willebrand factor was assessed using enzyme-linked immunosorbent assays. In our laboratory, the intra-assay coefficient of variation was 8.8%. No reference range available.
	RS	Von Willebrand factor antigen was measured with an in-house ELISA with polyclonal rabbit anti-human vWF antibodies (DAKO). The intra-assay CV was 1.9%, inter-assay CV was 6.3%, and the reference range was 0.60-1.40 U/ml.
	Twins UK	Von Willebrand factor was measured using an in-house sandwich ELISA.

Supplemental Table S2. Genotyping and imputation methods for autosomal chromosomes by study

	ARIC	B58C	CHS	FHS	RS
Methods					
Platform	Affymetrix	Affymetrix	Illumina	Affymetrix	Illumina
Chip	6.0	500K	370 CNV	500K + 50K	550 v3
SNPs investigated	906,600	490,032	306,655	490,700 (500K) 48,195 (50K)	561,466
SNP exclusion criteria*					
Call rate	≤0.90	1.00	≤0.97	≤0.97	≤0.98
HWE p-value	$<1.0x10^{-6}$	$<5.0x10^{-7}$	$<1.0x10^{-5}$	<1 x 10E-6	$<1.0x10^{-6}$
Variants included for imputation	602,642	490,032	291,322	343,361 (500K) 34,841 (50K)	512,349
Percent of variants included	66%	100%	95%	70% (500k) 72% (50K)	91.3%
Imputation software	MACH	IMPUTE	BIMBAM	MACH	MACH
Imputation software version	1.0.16	0.1.3	0.99	1.0.15	1.0.15
Genome build	35	35	36	36.2	36
Total number of SNPs	2,516,203	2,236,936	2,543,887	2,543,887	2,543,887
Population					
Total number of subjects in cohort(s)	15,792	1,461	5,888	16,419	7,983
Participants eligible for scans**	11,433[†]	1,461	3,980[†]	9,274	6,449
Percent eligible	72%	100%	68%	56%	81%
Participant with successful scans***	10,651[‡]	1,461	3,868[‡]	8,756	5,974
Percent successful	93%	100%	97%	94%	93%

HWE = Hardy-Weinberg equilibrium

*For CHS, >1 duplicate error or Mendelian inconsistency (for reference CEPH trios), heterozygote frequency = 0, SNP not found in dbSNP.

**ARIC number indicates the number of participants with available scans at the time of the analysis.

***Sample successfully genotyped on platform with within-participant variant call rate >0.95 and after implementation of all quality controls.

[†]European ancestry participants in ARIC (8861) and in CHS (3397)

[‡]European ancestry in ARIC (8127) and in CHS (3295)

Supplemental Table 3a. Replication cohort specific results for the top loci associated with factor VII activity and antigen

			ARIC (FVII:c)		Twins UK-1 (FVII:ag)		Twins UK-2 (FVII:c)		PROCARDIS (FVII:ag)	
CHR	SNP	Variant	β	P-value	β	P-value	β	P-value	β	P-value
2	*rs*1260326	C→T	1.1	2.6×10^{-1}	5.3	6.2×10^{-4}	2.0	1.4×10^{-1}	3.2	1.4×10^{-1}
4	*rs*1126670	T→G	-2.5	1.8×10^{-2}	1.2	4.6×10^{-1}	-1.5	3.1×10^{-1}	-2.2	3.2×10^{-1}
11	*rs*11230180	G→T	2.3	2.1×10^{-2}	1.5	3.4×10^{-1}	3.5	1.2×10^{-2}	2.1	3.2×10^{-1}
20	*rs*867186	A→G	7.1	2.0×10^{-5}	7.0	7.1×10^{-3}	4.8	3.8×10^{-2}	4.6	1.4×10^{-1}

Supplemental Table 3b. Replication cohort specific results for the top loci associated with von Willebrand factor antigen.

			ARIC		B58C		Twins UK (1 and 2)		VIS		Orcade	
CHR	SNP	Variant	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
6	*rs*9390459	G→A	-3.3	3.3×10^{-2}	-3.4	3.5×10^{-3}	-3.3	7.5×10^{-2}	-2.7	1.9×10^{-1}	-4.4	2.2×10^{-2}
8	*rs*2726953	C→T	5.5	1.4×10^{-3}	2.7	2.9×10^{-2}	2.1	3.1×10^{-1}	6.0	1.3×10^{-2}	0.7	7.2×10^{-1}
12	*rs*4981022	T→C	-5.0	6.0×10^{-3}	-3.6	2.1×10^{-3}	0.1	7.2×10^{-1}	-10.2	5.7×10^{-5}	-3.6	9.5×10^{-2}
12	*rs*7978987	G→A	3.4	4.4×10^{-2}	0.0	9.9×10^{-1}		NA	0.9	6.8×10^{-1}	0.9	6.4×10^{-1}
14	*rs*10133762	G→T	4.0	1.1×10^{-2}	1.8	1.2×10^{-1}	0.2	9.3×10^{-1}	5.1	9.5×10^{-3}	5.3	4.6×10^{-3}
19	*rs*868875	A→G	-0.5	7.9×10^{-1}	-2.8	2.3×10^{-2}	-25.6	5.0×10^{-1}	1.6	6.4×10^{-1}	-6.9	1.3×10^{-1}

CHR = chromosome; P = p-value; β coefficient represents change (% of activity or antigen) associated with 1-unit change in allele dosage; NA = parameter estimate not available; SNP = single nucleotide polymorphism.

Supplemental Table S4. Minimum detectable percent changes in hemostasis factor with at least 80% power according to minor allele frequency

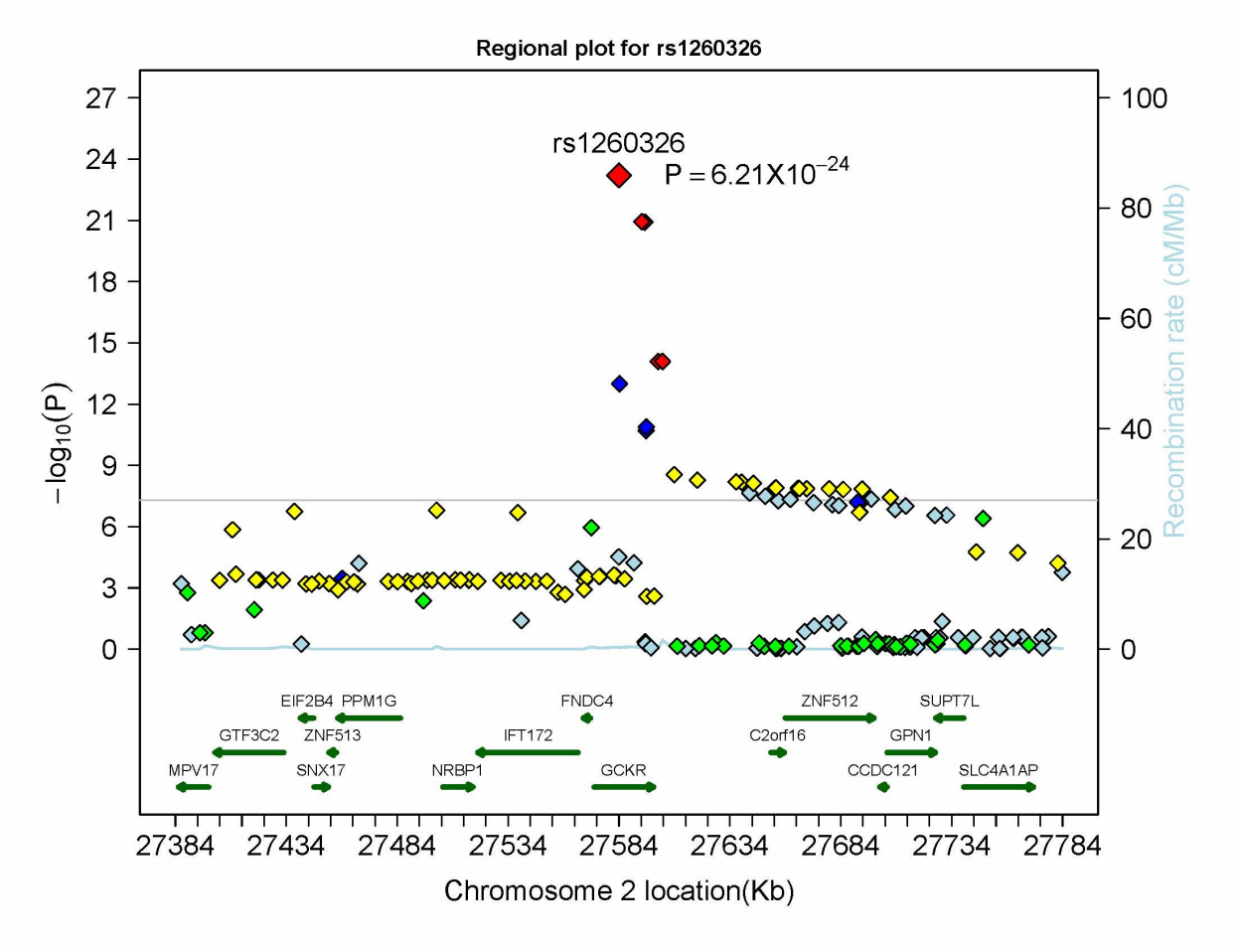
MAF	FVII mean = 100%, SD = 30% (n= 15400)	FVIII mean = 100%, SD = 35% (n=15200)	vWF mean = 100%, SD = 45% (n=17600)
5%	5.0%	6.0%	7.0%
15%	3.0%	4.0%	4.5%
25%	2.5%	3.0%	3.5%
35%	2.5%	3.0%	3.5%

MAF = minor allele frequency;

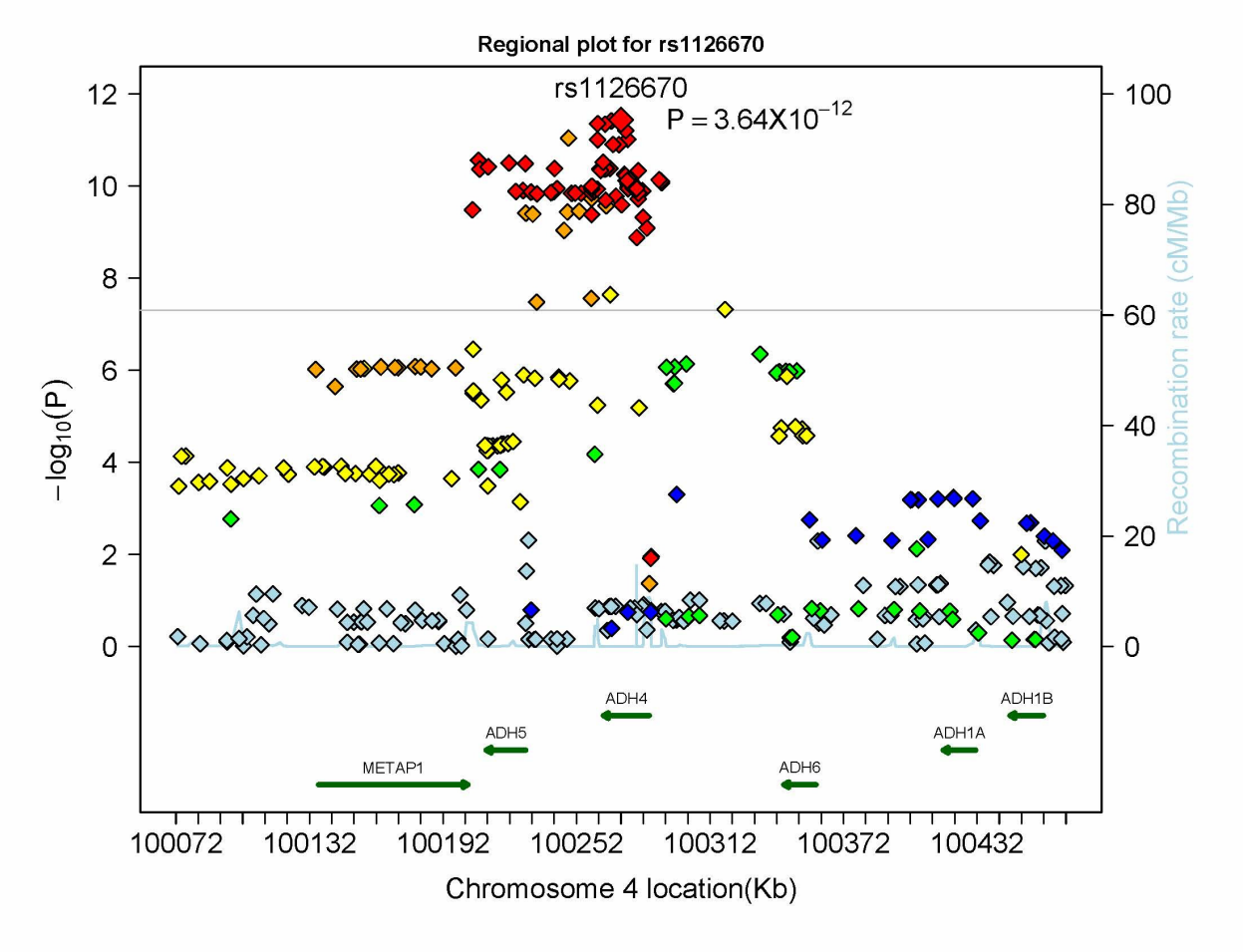
Figure Legend

Supplemental Figures S1-S13. Regional plots for top marker loci. The top SNP is presented as a large diamond in red font and neighboring variants are presented in different colors based on linkage disequilibrium based on HapMap Caucasian data: red: $1 \geq r^2 > 0.8$; orange: $0.8 \geq r^2 > 0.6$; yellow: $0.6 \geq r^2 > 0.3$; green: $0.3 \geq r^2 > 0.1$; blue: $0.1 \geq r^2 > 0.05$; light blue: $0.05 \geq r^2 > 0.0$. The left y-axis is the p-value on the $-\log_{10}$ p-value scale and the gray line marks the threshold of genome-wide significance, $5x10^{-8}$. The right y-axis is the recombination rate in centimorgans per mega base and the light blue line maps the rate across the region. Regional genes and their direction of transcription are depicted with green arrows.

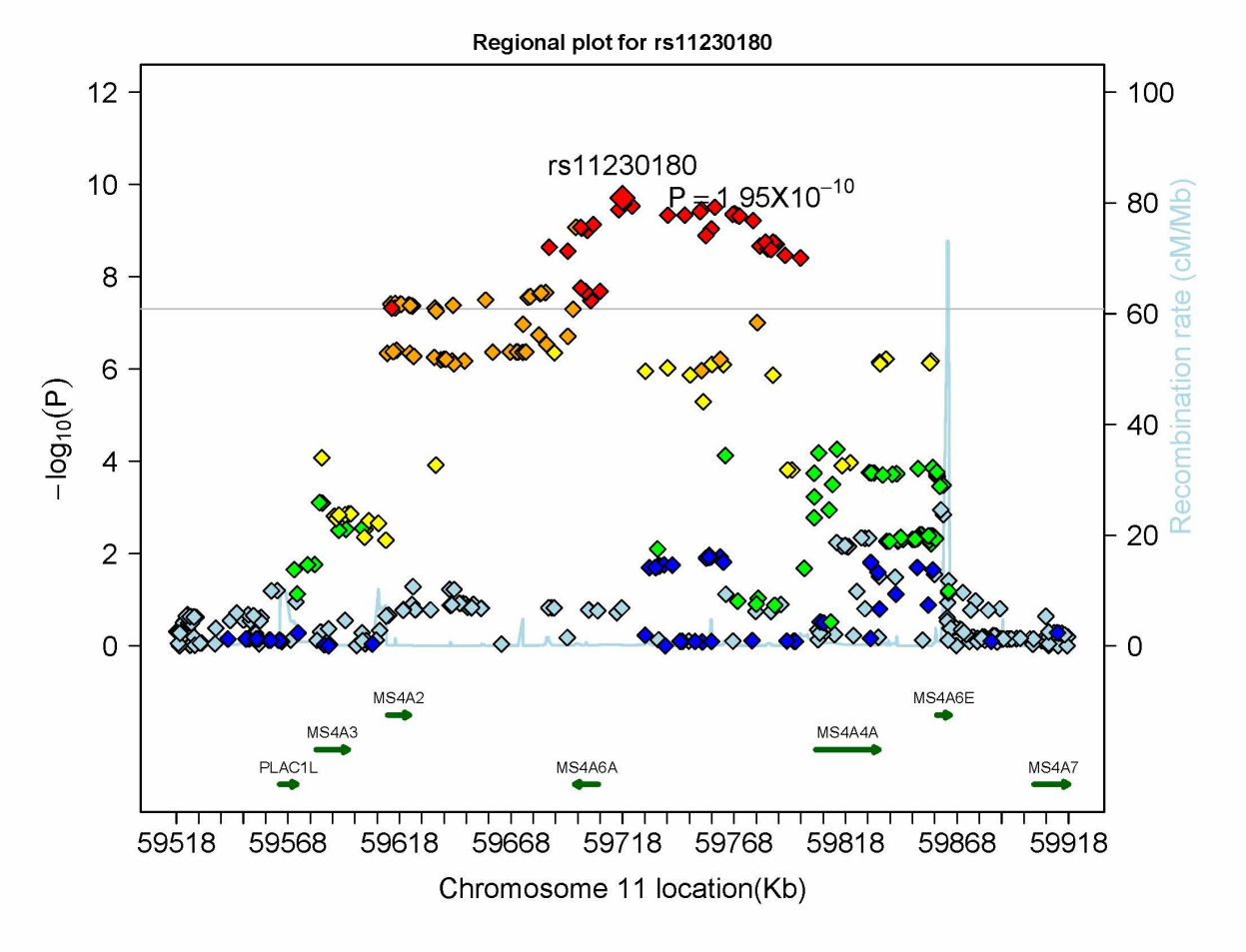
S1. *rs*1260326



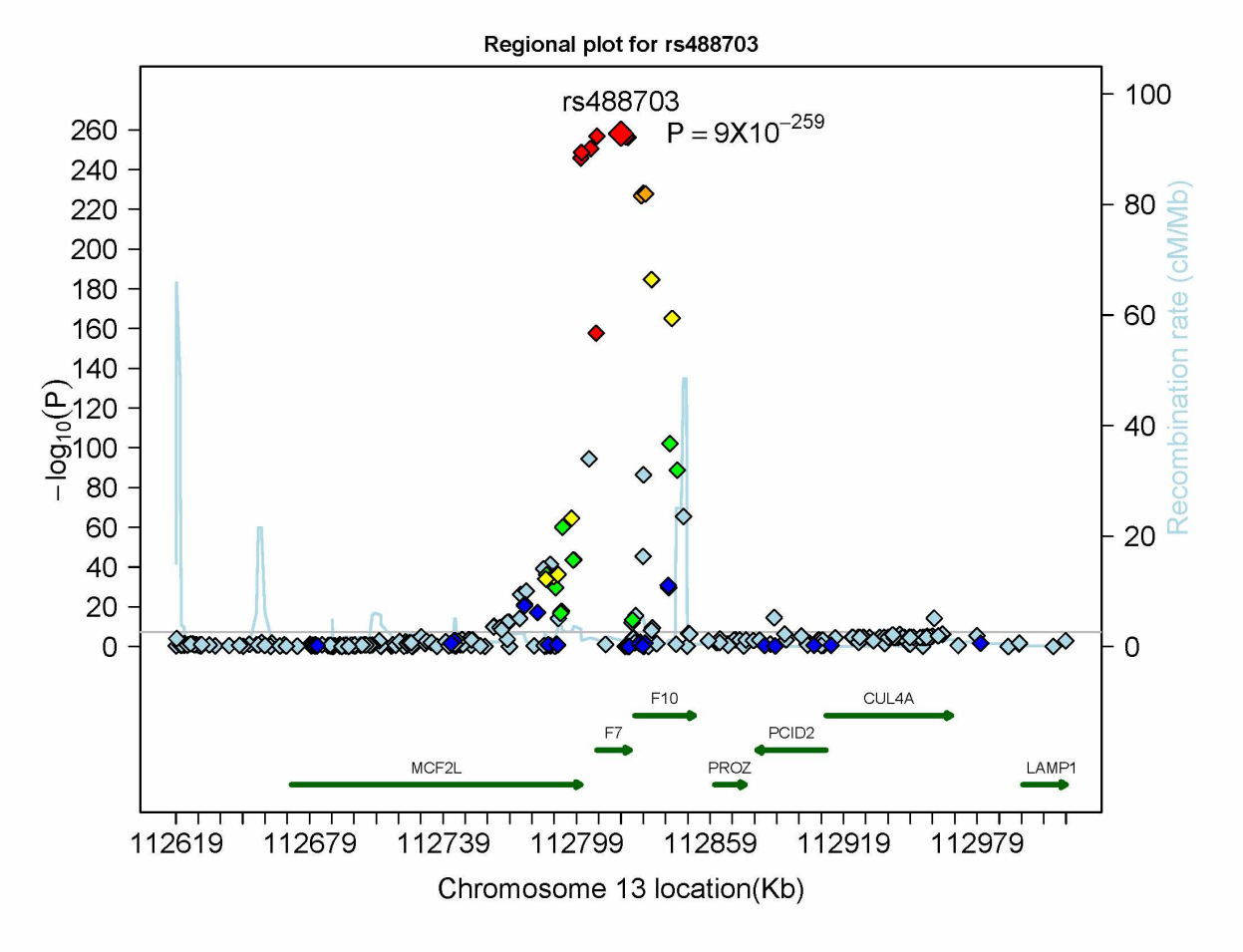
S2. *rs*1126670



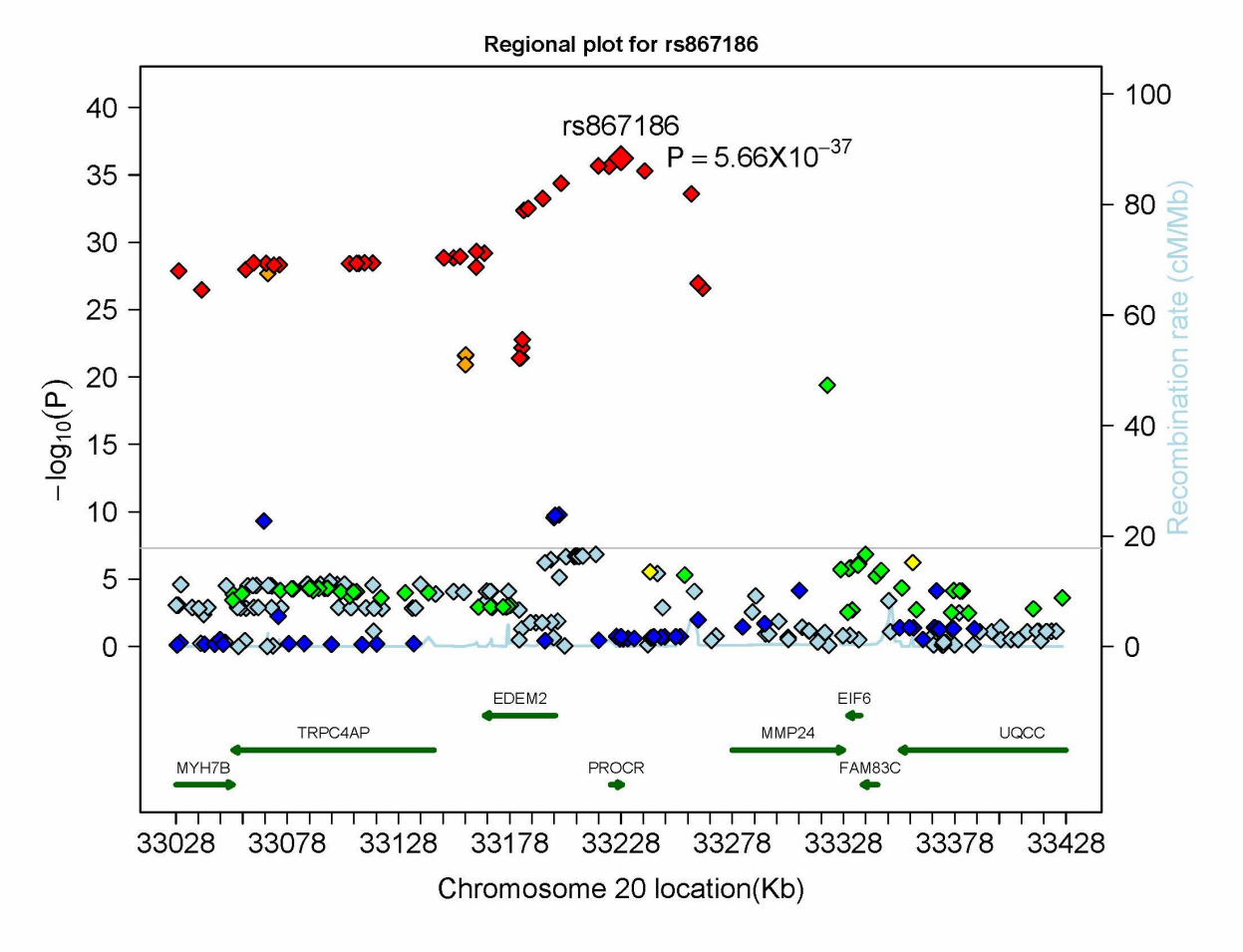
S3. *rs*11230180



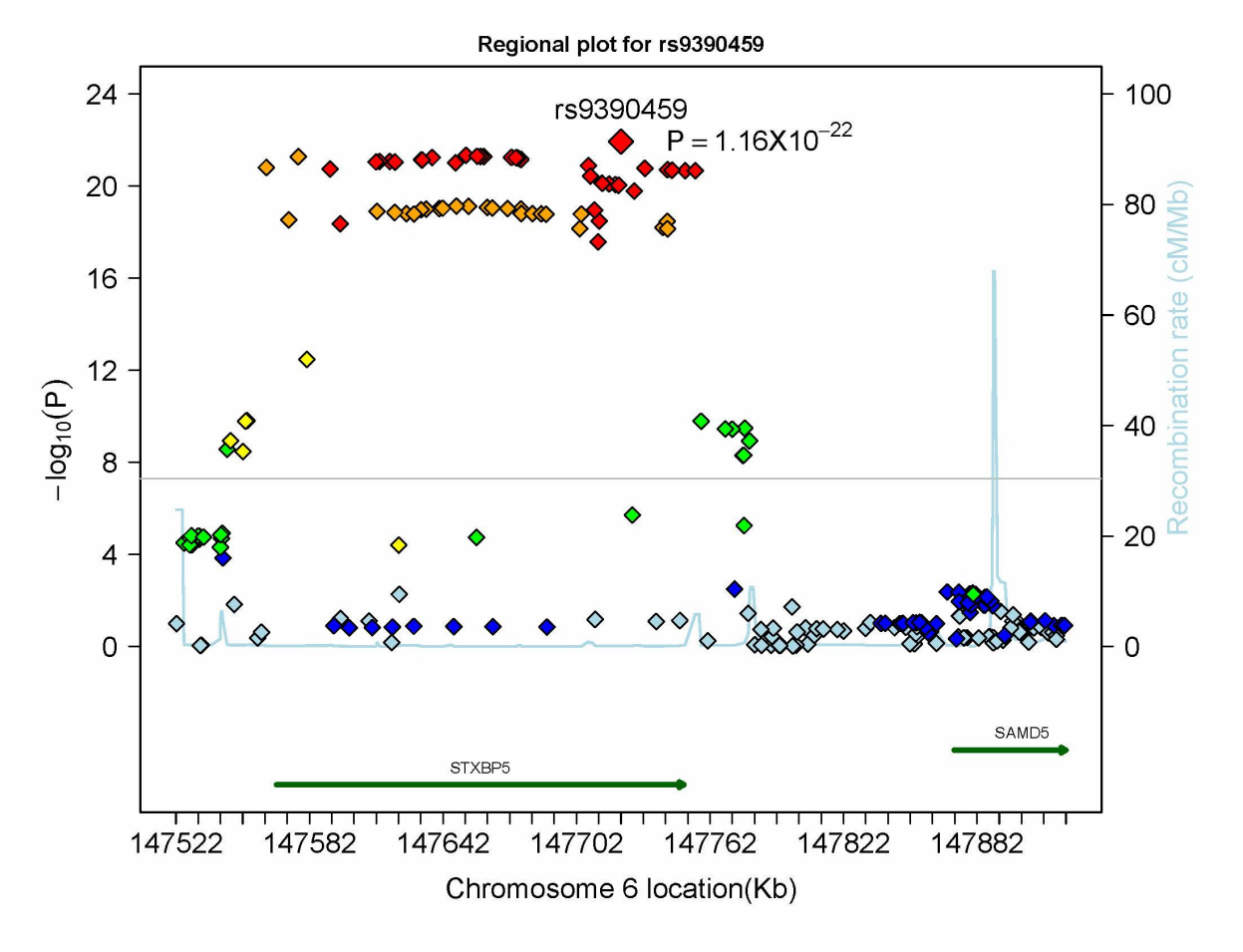
S4. *rs*488703


Regional plot for rs488703
rs488703
P = 9X10−259
−log10(P)
Recombination rate (cM/Mb)
F10
CUL4A
F7
PCID2
MCF2L
PROZ
LAMP1
112619
112679
112739
112799
112859
112919
112979
Chromosome 13 location(Kb)

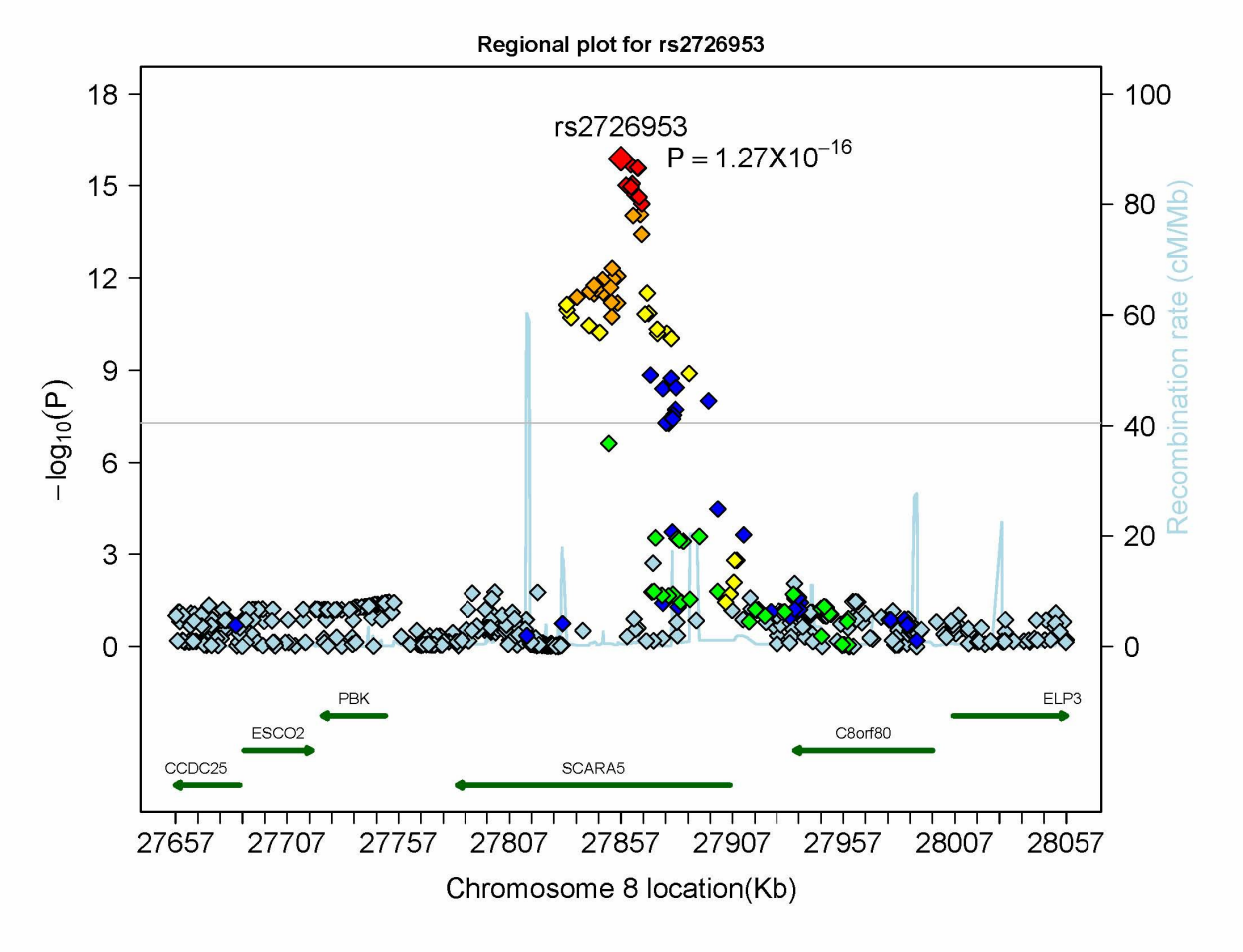
S5. *rs*867186


Regional plot for rs867186
rs867186
P = 5.66X10−37
−log10(P)
Recombination rate (cM/Mb)
EDEM2
EIF6
TRPC4AP
MMP24
UQCC
MYH7B
PROCR
FAM83C
Chromosome 20 location(Kb)

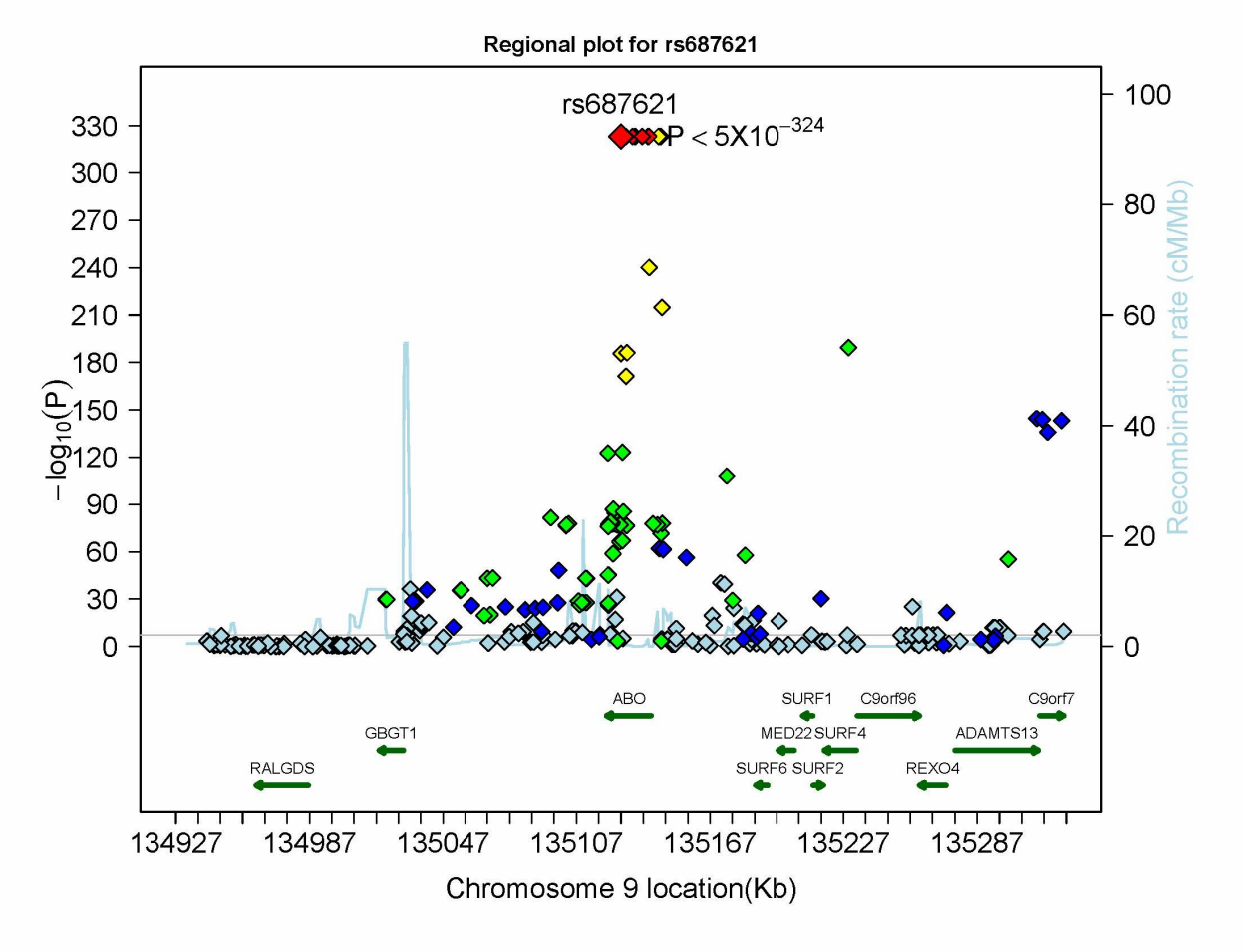
S6. *rs*9390459



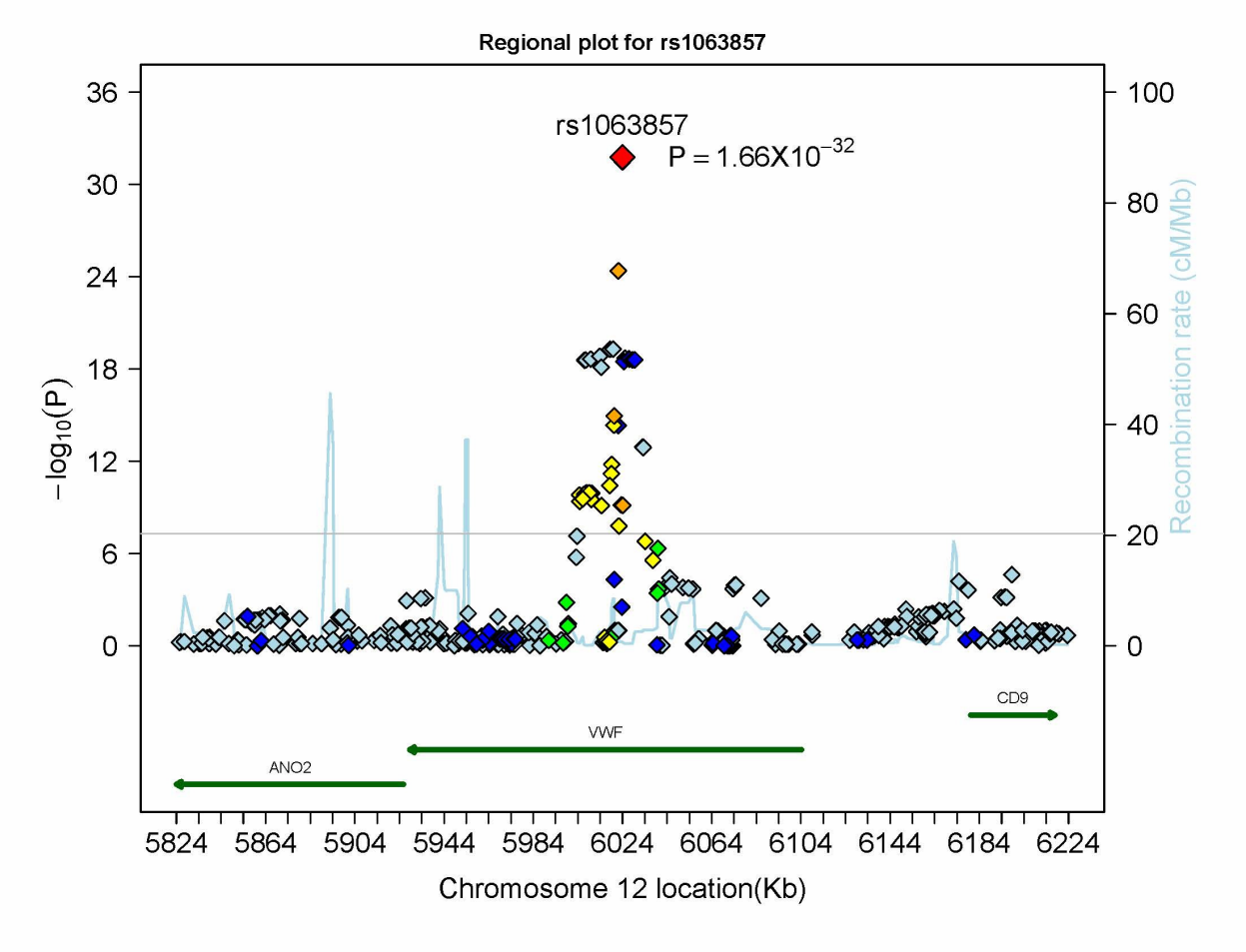
S7. *rs*2726953



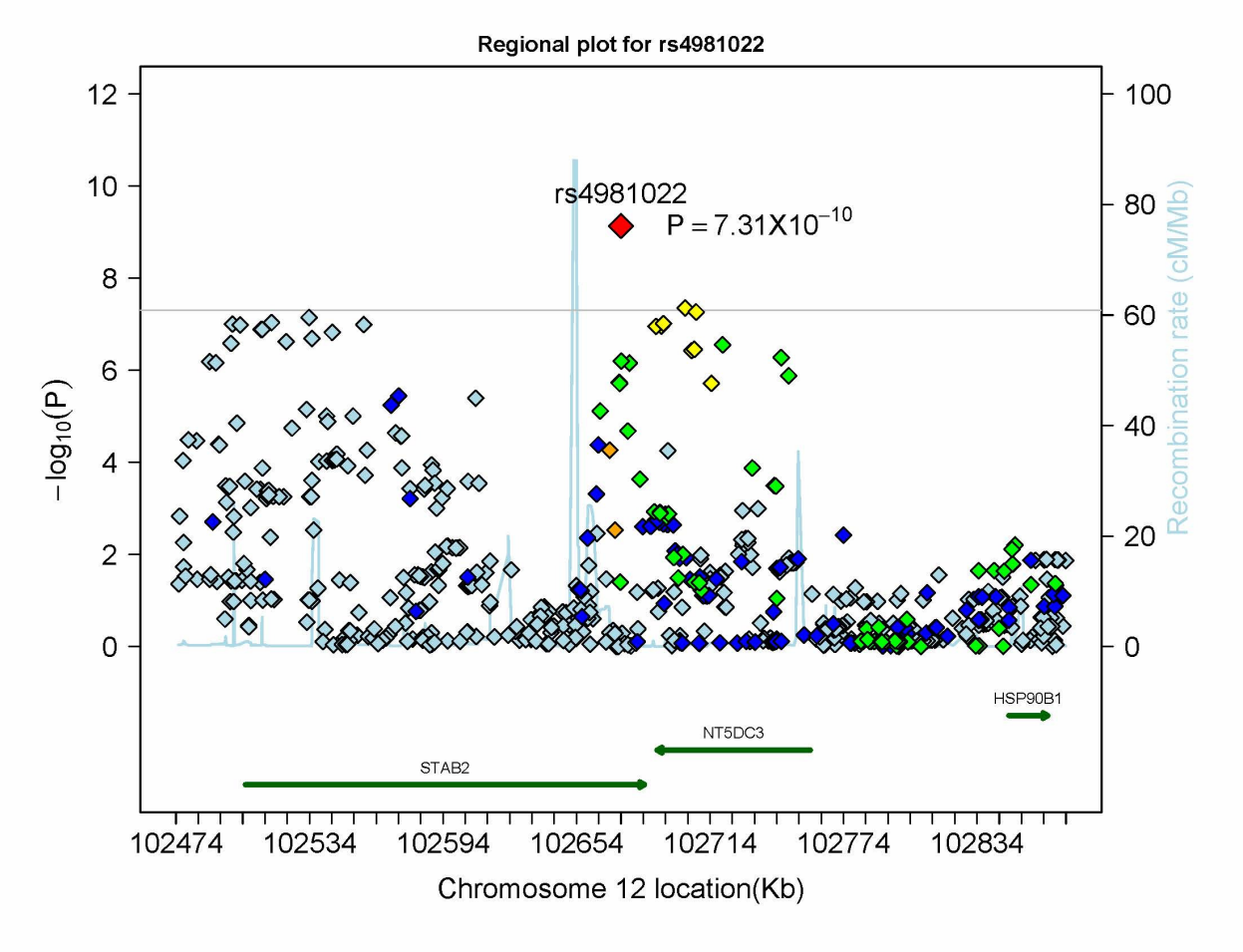
S8. *rs*687621


Regional plot for rs687621
rs687621
P < 5X10−324
330
300
270
240
210
180
150
120
90
60
30
0
−log10(P)
100
80
60
40
20
0
Recombination rate (cM/Mb)
ABO
SURF1
C9orf96
C9orf7
GBGT1
MED22
SURF4
ADAMTS13
RALGDS
SURF6
SURF2
REXO4
134927
134987
135047
135107
135167
135227
135287
Chromosome 9 location(Kb)

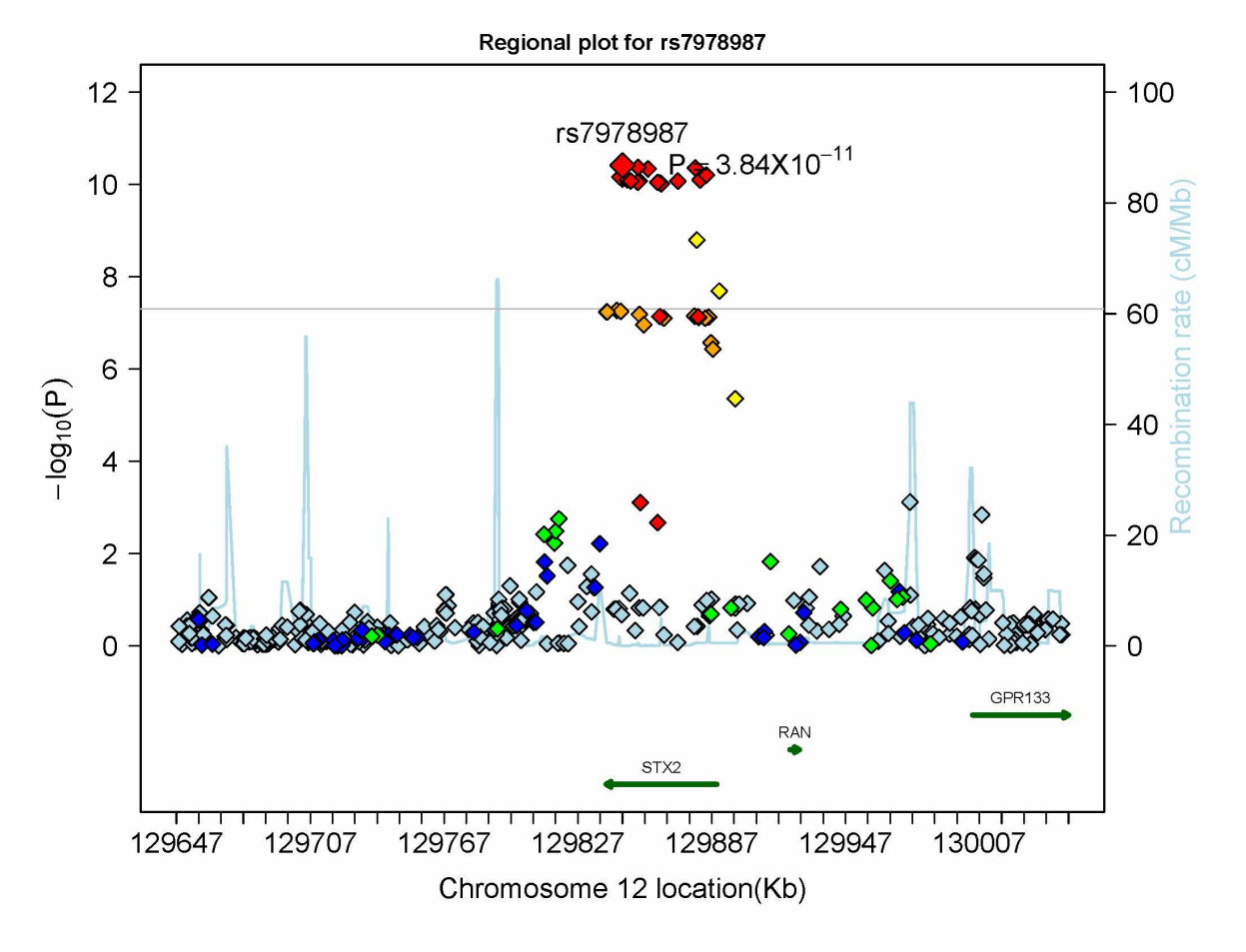
S9. *rs*1063857



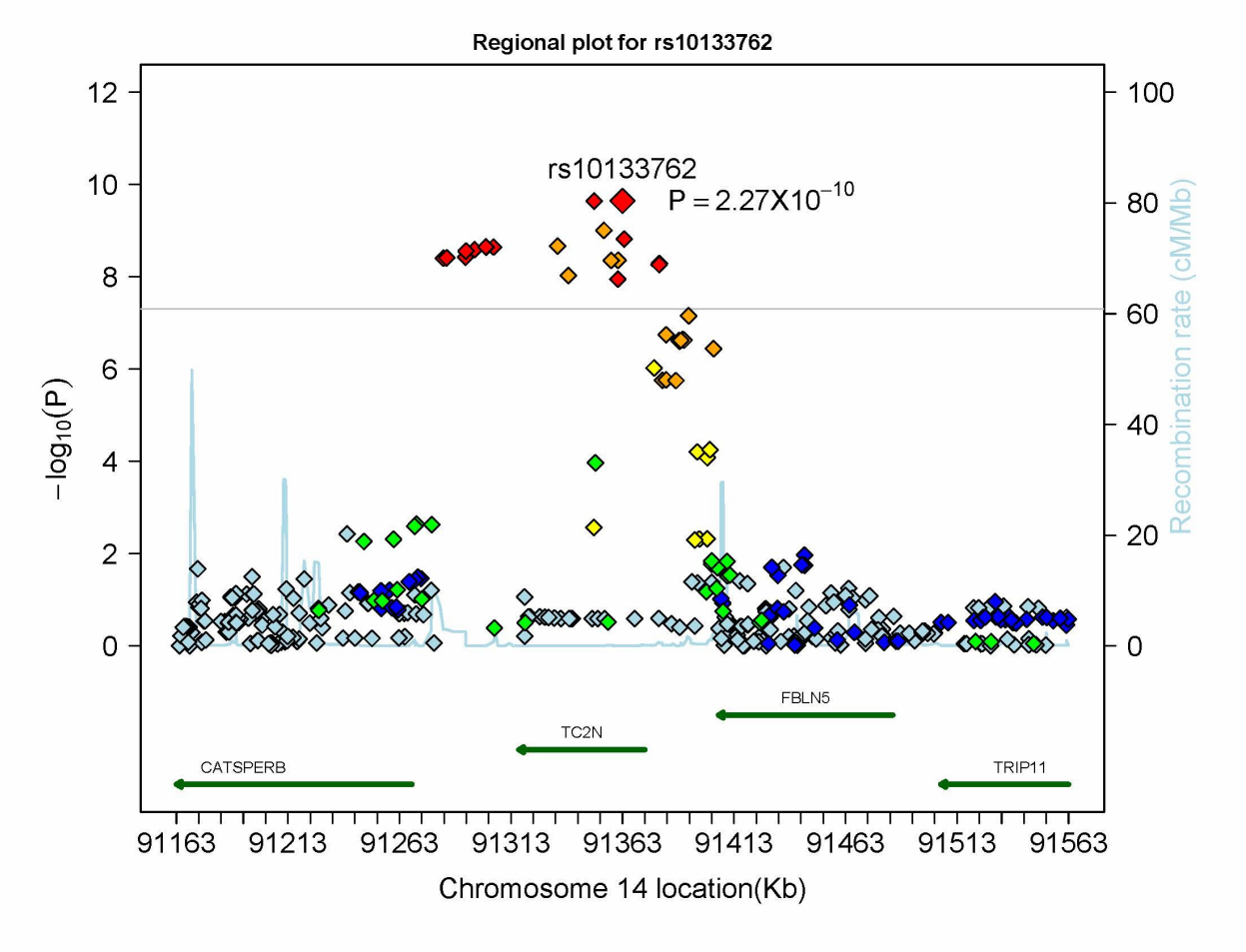
S10. *rs*4981022



S11. *rs*7978987



S12. *rs*10133762



S13. *rs*868875